DEVELOPMENT AND EVALUATION OF ALTERNATIVE DOSAGE FORMS OF METFORMIN AND ITS COMBINATION FOR GERIATRIC PATIENTS

SUMMARY FOR THE DEGREE OF

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Table of Content:

Sr. No.	Topics	Page No.
1.	Introduction	3-4
2.	Rationale	4
3.	Objectives	5
4.	Research Work	5-38
5.	Summary	38
6.	Publications, Presentation and Patent applications	39-40
7.	References	40-42

1. INTRODUCTION

Diabetes mellitus has been a significant challenge in the 21st century. It is estimated that by 2040, about 64 million or one in every 10 adults are likely to be affected by diabetes. Researchers have developed several orally administered anti-hyperglycemic drugs with various modes of action to lower the levels of glucose and further delay the possibility of serious complications in diabetic patients (Diabetesatlas.org. 2021). Metformin hydrochloride (MH), a biguanide, has been used for the past several years for the type 2 diabetes treatment. Its mode of action includes reducing basal and postprandial glucose levels in plasma in type 2 diabetics, leading to enhanced glucose tolerance. It additionally, lowers absorption of glucose in intestine as well as hepatic glucose synthesis. It increases peripheral glucose uptake, its utilization and therefore, improves the insulin sensitivity. MH is believed to have become the world's most widely prescribed antidiabetic drug. However, for a few patients, monotherapy using single drug is not sufficient to reduce the glucose level. To overcome this barrier, antidiabetic drugs having different mode of actions and/or their combinations are advisable for type 2 diabetes [M. Salim et al. 2012, P. Shah et al. 2016). Teneligliptin hydrobromide hydrate (THH), a DPP-4 inhibitor, shows rapid absorption, and biphasic elimination. Its steady state reaches in 5 days after first dose of 40 mg a day administered (Y. Nakamaru. 2013). THH's unique structure involves five consecutive rings (J-shaped) that may be responsible for its potency and half-life. THH became popular DPP-4 inhibitor among prescribers in countries like India in a very short span from the time it entered the market. Its safety and efficacy has also been demonstrated in populations of Japan, China and Korea through many randomized controlled clinical trials (T. Eto et al. 2012, L. Scott. 2015, W. Wu et al 2015). These combinations have proven beneficial in terms of better patient compliance, less contraindications, having lesser risk for hypoglycemia and increasing body weight. These combinations can be useful for both acute as well as chronic treatment.

A few tablets formulations of MH in immediate and extended release form, as well as a few tablets of THH in immediate release form and MH in sustained release form are available in the Indian market. However, their unit sizes are very large due to average weights of unit doses. Commercially available capsule shaped bilayered tablets of THH 20 mg and MH 1000 mg tablets have more than 20 mm length and more than 10.5 mm width. Such large tablets

can lead to difficulty in swallowing (dysphagia). This occurs primarily in elders due to age related changes in gastrointestinal tract. Some individuals undergoing such therapy refuse to continue the treatment because swallowing becomes too painful for them (Stegemann et al. 2012; Payot et al. 2011).

Considering the issues faced related to swallowing of large sized and specific shaped tablets and capsules, USFDA published guidance in June 2015 named "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" for generic products (Guidance for industry 2015). As a regulatory requirement, generic products to be marketed in USA are required to have pharmaceutical and therapeutic equivalence to Reference Listed Drugs. Also they are recommended to be similar in physical attributes with respect to reference product. It is evident from resources available; researchers have followed following approaches to deal with large size dosage forms by changing to different dosage forms , crushing tablets/opening of capsules, use of better swallowing techniques, providing technologies for application of coating at consumer end, using swallowing aids, changing to different salt of drug substance to manage solubility and dosage form size.

2. RATIONALE

USFDA, **c**onsidering the issues faced related to swallowing of large sized and specific shaped tablets and capsules, published a guidance on size/shape of tablets and capsules in June 2015. According to this guidance, any new generic manufacturer introducing product in US market, needs to consider the size and shape recommendations as per this guidance, apart for other regulatory requirements stated in 21 CFR. The initiative taken by USFDA is anticipated to be applied for other countries since it will help the global population.

The difficulty in swallowing large size dosage form is also observed in younger population. There is an another guidance document published by USFDA regarding size of beads in sprinkle dosage form, "Size of Beads in Drug Products Labeled for Sprinkle" (Guidance for Industry 2012).

The proposed work is directed towards resolving practical problems by developing alternatives against larger size tablets dosage form of MH and its combination for geriatric patients.

3. OBJECTIVES

- To select marketed formulation for geriatric population anticipated to pose swallowing difficulty.
- To attempt various formulations based on different manufacturing technologies against selected marketed formulations.
- To develop appropriate analytical method and to perform validation of analytical methods.
- To characterize and optimize the formulations to achieve comparable in vitro dissolution profiles in multi media.
- To perform stability studies as per ICH guidelines in primary packs.
- To do process optimization to achieve robust process for optimized formulations.
- To perform in silico evaluation of developed products against reference products using GastroPlus software.

4. RESEARCH WORK

The research was carried out for developing alternative dosage forms to large size tablets of MH and its combination. Additionally, two dosage forms were discontinued during development. The course of development involved literature review, patent and other intellectual property rights searches, patentability possibilities evaluation, selection of excipients and sourcing of various components including reference products for comparison, preformulation studies, feasibility trials experimentations, optimizing formulations with DOE software wherever possible, analytical method development and validation, in silico evaluation using GastroPlus software, scale up of pellets process, stability studies as per ICH conditions and presentation/publication of the research work.

4.1 Analytical method development

4.1.1 MH dosage forms

Assay method as per USP monograph of Metformin Hydrochloride Tablets was referred. This is an UV method with maxima at 232 nm. During validation of this method, specificity, linearity (50% to 150%) and recovery (at 50%, 100% and 150% level) were completed.

Dissolution test is also an UV method, referred from USP monographs. During validation of this method, specificity, linearity (10% to 150%) and recovery (10% to 150% levels) were completed. Paddle method at 50 rpm was used for jelly formulation and basket method at 100 rpm was used for pellets formulation.

Related substances method as per in house developed method was evaluated and found suitable. During validation of this method, specificity, linearity (LOQ level to 150% for 1-Cyanoguanidine and MH) and recovery (LOQ level to 150%) were completed.

4.1.2 THH dosage forms

Analysis of assay, related substances and dissolution of Teneligliptin Tablets IP monograph is by HPLC method. Assay method of in this monograph was not found to be suitable for dosage forms developed. There was an interference of MH at RT of THH. Hence in house method was developed and was found suitable. During validation of this method, specificity, linearity (50% to 150%) and recovery (at 50%, 100% and 150% level) were completed.

We referred chromatographic conditions used for in house developed assay method, for dissolution testing of THH from the oral jelly and sachets containing THH granules. During validating this method, specificity, linearity (10% to 150%) and recovery (at 10% to 150% level) were completed.

Related substances method as per IP monograph of Teneligliptin Tablets could not be useful as interference at Teneligliptin RT was observed from the placebo of Combination jelly. Hence, in house developed method was evaluated and it was found useful. During validation of this method, specificity, linearity (LOQ level to 150% for Impurity A and THH)and recovery (LOQ to 150% of known impurity limit) was completed.

4.2 Formulation development

The detailed development and evaluation work was carried out for following products:

4.2.1 Oral jelly of MH,

4.2.2 Teneligliptin Oral Jelly Containing MH Extended Release Pellets,

4.2.3 MH Immediate Release Pellets,

4.2.4 MH Extended Release Pellets and

4.2.5 Blend containing granules of THH in immediate release form and MH pellets in extended release form.

4.2.1 Development and evaluation of oral jelly of MH

An alternative to large size tablets of MH in terms of oral jelly was selected for development. The reason behind not selecting liquid dosage form for development was to acknowledge the fact stated herewith. Even though the liquid dosage forms have ease for swallowing, the dysphagic patients may experience aspiration and coughing at the time of swallowing such less viscous fluid products (N. Barnett. 2016, H. Ninomiya. 1999).

Oral jellies as a dosage form, are packed in unit pouches which are travel-friendly, user-friendly in terms of self-administration and therefore can have better patient compliance. Additionally, they can be consumed without using any fluid and without any difficulty in swallowing, therefore are preferable for geriatric patients over dosage forms like tablets (K. Prakash et al. 2014, S. Miyazaki et al. 2009).

Looking at the commercial strengths available, we worked on 500 mg, 850 mg and 1000 mg strengths. The experimental trials and optimization of oral jelly was carried out by use of Design of Experiments (DOE) statistical method.

MH is bitter in nature, therefore the challenging part for this oral jelly formulation would be the palatability. As this drug is used in treatment of diabetes mellitus, the use of sugar is obviously avoided. Instead, a set of artificial sweeteners including sucralose, neotame, thaumatin, acesulfame potassium, sodium saccharin and aspartame was evaluated in the experimental trials. In this sugar free formulation, sucralose was pursued as an artificial sweetener, propylene glycol as cosolvent and sodium carboxymethyl cellulose (sodium CMC) as viscosity increasing agent. It was thought to give an elegant look to the formulation using water soluble sunset yellow colour. Mango orange flavour was selected to increase the palatability of the formulation. This flavour matched the perception of the colour of the formulation.

It was decided to use triple laminated sachet as primary packing material having configuration polyester/aluminium/polyethylene. This would enable patients to carry the unit dose in pockets or in purses.

For optimizing the formula, three factors were considered for optimization of the formulations viz. quantity of sucralose (0.8% w/w – 1.6% w/w), quantity of propylene glycol (2% w/w– 14% w/w) and quantity of sodium CMC (0.6% w/w– 1.8% w/w). The optimization trials were chalked out by using a 2 level full factorial design of experiment with four centre

points, through software Design Expert version 11 from Stat-Ease Inc. giving rise to 12 randomized experiments. This design was analysed for different statistical parameters to study interaction effect and ANOVA parameters, such as curvature if it is present, calculation and interpretation of p value, if model is significant and to arrive at design space.

The outcome of the experiments was studied in terms of responses or results viz. viscosity, pH, transparency, taste masking and refractive index. The statistical software was used to analyse individual response parameters such as significant effects (Pareto chart), ANOVA parameters, and different types of model graphs.

A simple manufacturing process was involved with a specific sequence of addition as important steps. It involved dissolving MH and sucralose in 80% w/w of total purified water for the batch using an over head stirrer (make: Remi motors (India)). In this solution, sodium CMC was added slowly with constant stirring to form a consistent jelly. Flavour was mixed in propylene glycol and added to the viscous solution formed, with continuous stirring. Colour was dissolved in purified water and added to the bulk solution with constant stirring. Finally, weight was made up with purified water, stirring was continued for 10 minutes to form final jelly. The target weight for 1000 mg strength was kept 5 g. Likewise, target weight for 500 mg was kept 2.5 g and that for 850 mg strength was kept 4.25 g, since the lower strengths would be dose-weight proportional.

The optimized formulation was charged for stability as per ICH condition (accelerated conditions of 40°C/75% RH and long term conditions of 30°C/75% RH and 25°C/60% RH) in triple laminated unit sachets for 500 mg/5 g and 1000 mg/5 g strengths.

Physico-chemical evaluation involved the measurement of viscosity of 250 mL formulation at 25°C, using Brookfield viscometer (model: DVII + Pro) with spindle number LV-2 (62), LV-4 (64) and T bar spindle no. 96 with helipath assembly, to cover viscosity range between 2919 cps and 102519 cps of various experiments. Triplicate readings were taken, at various RPM. A single value near torque value 50 was used to process the data in software. For optimized formulation spindle no. LV-4 (64) was used.

pH meter, (make: Lab India) was used for measurement of pH of the experimental trials. The reading was taken in duplicate and average reading was considered for evaluation.

Visually the experimental trials were checked for transparency, and scoring as given from 1 to 5 scale. Oral jelly was taken in a test tube and viewed against a board with illuminated

white and black background. The clear transparent jelly was given the highest score of 5 and least transparent or hazy jelly was given score of 1.

All 12 experimental trials were evaluated for taste masking through scoring from 1 to 5 scale. Normal human volunteers (twelve) including both male and female subjects of age between 25 and 45 were selected for the taste trial. Score 5 would be for complete bitter taste masked formulation and 1 would be the most bitter formulation.

Refractive index was checked using Abbe's refractometer (make: Rajdhani Industries Ltd., model: RSR-1), to assess the property of the formulation.

MH jelly is not official in any pharmacopoeia. We referred conditions mentioned in monograph of MH tablets from United States pharmacopeia for dissolution test. MH jelly was weighed by difference and dissolution test was carried out using USP type 2 (Paddle) apparatus, using pH 6.8 $\pm$ 0.05 phosphate buffer, 1000 mL, 50 rpm, at 37 ± 0.5 °C. The analyte was measured using UV spectrophotometry (λmax of 232 nm); (Spectrophotometer make- Agilent Technologies Ltd, India).

For measurement of assay, sample equivalent to about 100 mg MH, collected from 5 sachets was weighed and diluted using water to get 10 ppm concentration. Standard solution of same concentration was prepared. The absorbance of standard and sample preparation was measured at 232 nm in 1 cm cell against water as blank using a UV spectrophotometer.

Related substances method of MH extended release tablets was referred from USP monograph and was used for evaluation of the oral jelly formulations, with minor modifications.

Responses in experiments were treated in the software to arrive at an optimized formulation.

Table 1 mentions the important significant effects observed, either individual or in combination of the three factors for the respective responses.

Table 1: Significant effects observed for different responses

Sr. No.	Responses	Significant Effects
1	Viscosity (cps)	A,AC, C
2	pH (numerical)	AB, AC, C
3	Transparency (score)	A, C
4	Taste masking (score)	C
5	Refractive index (numerical)	C

Note: A = sodium CMC, B = sucralose, C = propylene glycol, AB = Interaction of sodium CMC, sucralose, AC = Interaction of sodium CMC and propylene glycol

The 3 D graphs for the respective responses are as depicted in figure 1.

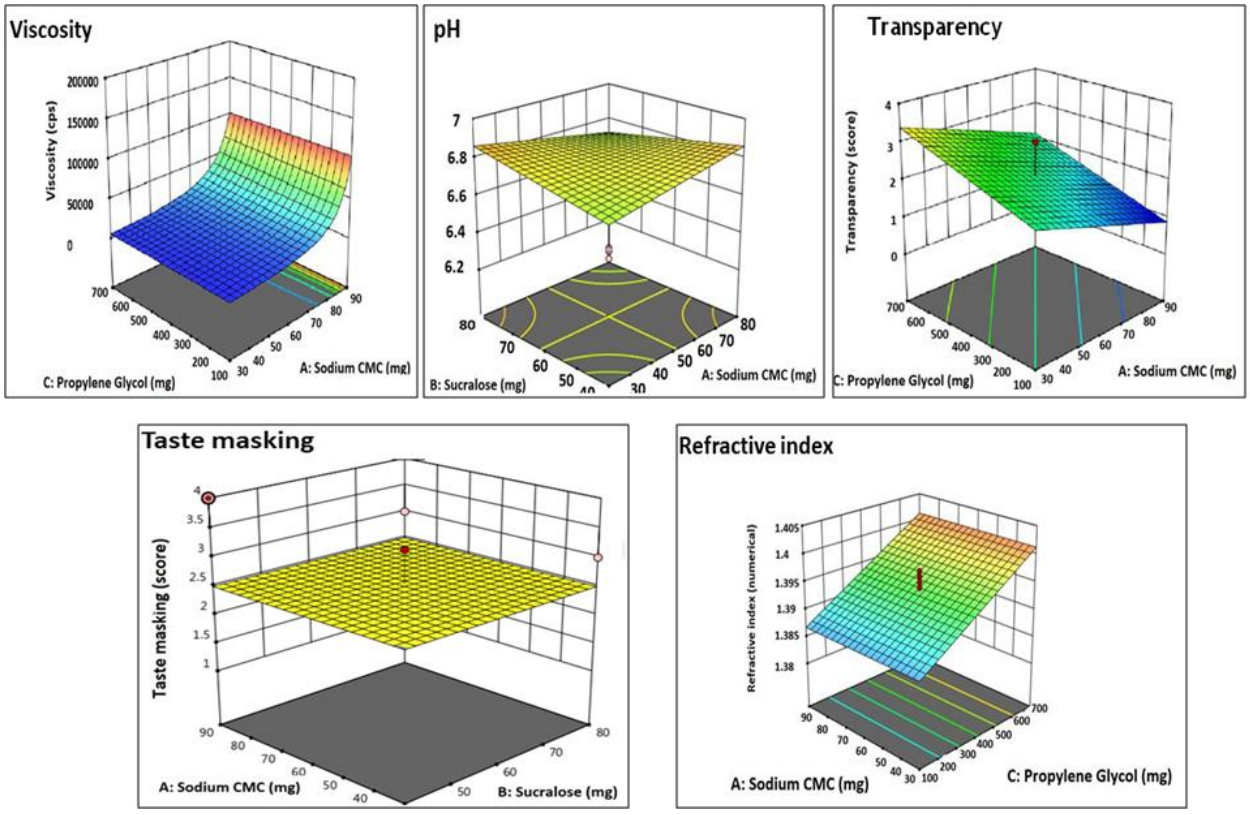


Figure 1: 3 D surface graphs of all responses

As indicated in the 3D graph, as concentration of sodium CMC increases from experimental values of 0.6% w/w to 1.8% w/w, the viscosity increases gradually upto 1.2% w/w concentration, but increases rapidly when concentration approaches 1.8% w/w. Such

curvature effect is seen for the response, pH also, whereas for other responses the effects are more or less in a straight plane, although at a specific slope.

When the threshold limits to have desired parameters are fed into the software and run the predictions, we get design space as mentioned in figure 2 to select optimized formulation.

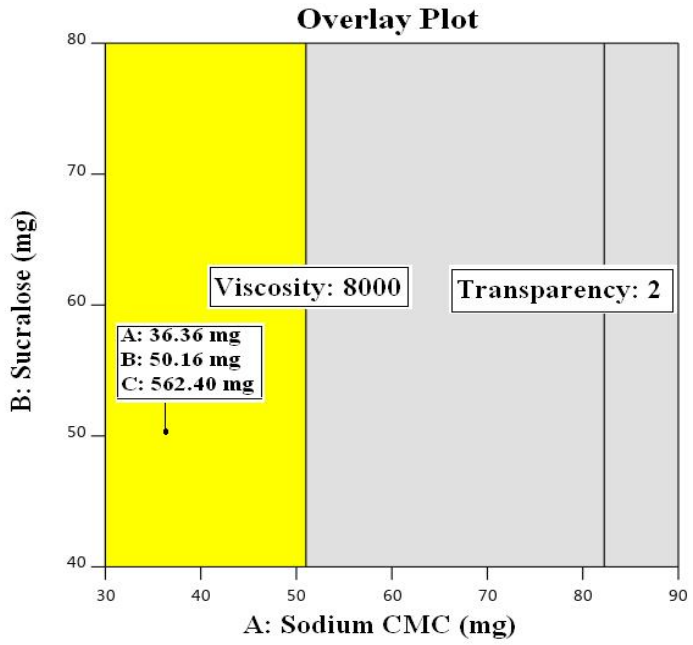


Figure 2: Design space for arriving at optimized composition of oral jelly of MH

The optimized formulation using design space was processed ahead for charging for stability. This optimized formulation was better especially in terms of taste masking, and was found to obey the predicted responses as per the design space.

The optimized formulation was subjected to in vitro release and was compared against MH tablets marketed in US market, the samples were gifted by Granules India Limited. The comparative dissolution profiles in pH 6.8 are shown in figure 3 for 1000 mg, 850 mg and 500 mg strengths in pH 6.8 phosphate buffer. For initial time points i.e. upto 30 min. faster dissolution was seen from jelly compared with tablets for 1000 mg and 850 mg strengths. This may be due to dissolved form of drug in jelly whereas tablets require some time to disintegrate. For 500 mg strength there was no significant difference between dissolution profiles of tablets and oral jelly, although, release from jelly was slightly faster till 20 min. this may be due to better sink condition achieved for lowest strength.

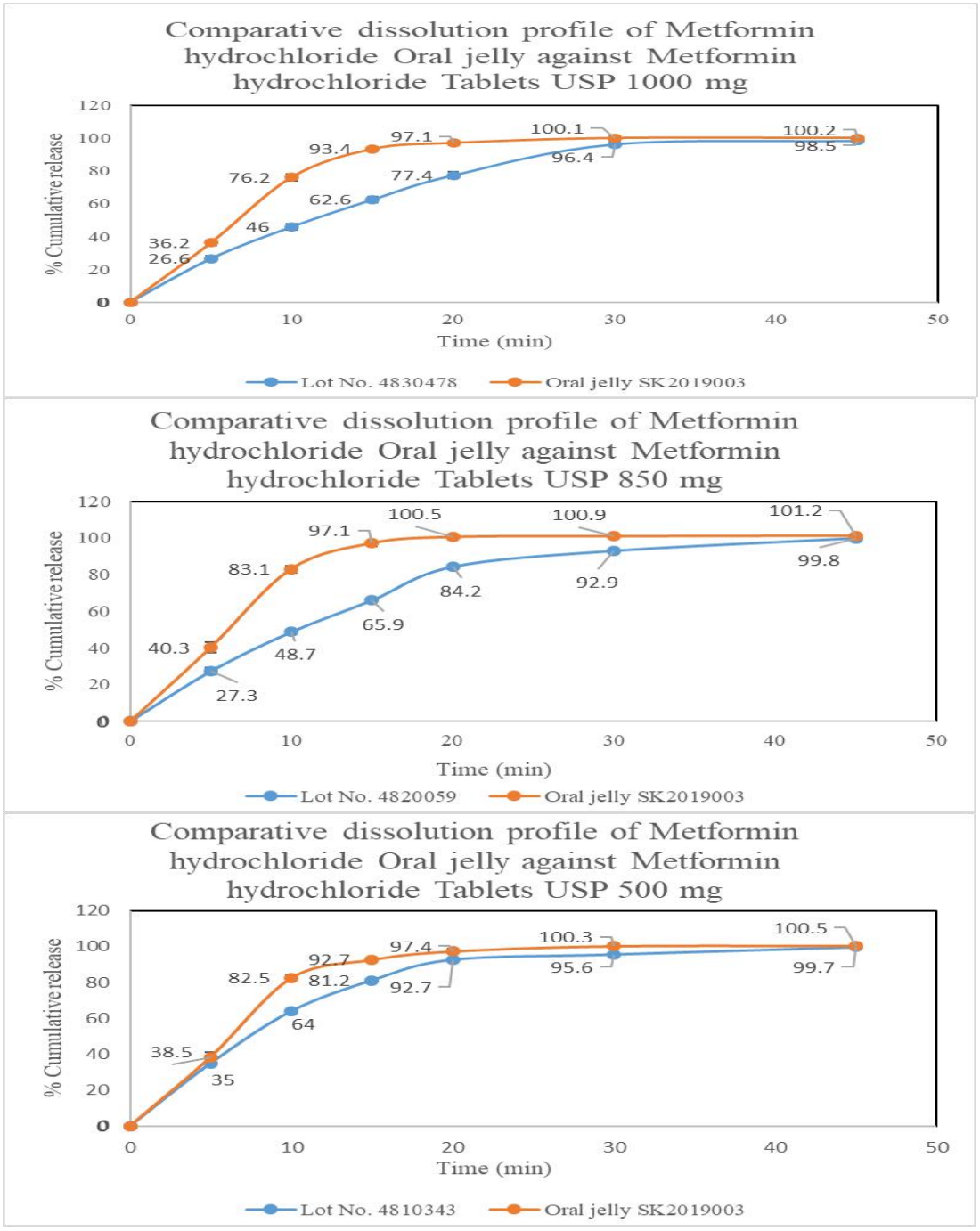


Figure 3: Comparative dissolution profile of marketed tablets vs. oral jelly for 1000 mg, 850 mg and 500 mg in pH 6.8 phosphate buffer

As observed from the dissolution rate graphs, both marketed formulations and prepared oral jelly of MH released the drug to complete extent.

Stability of the finished product:

The stability data indicates that there was no significant change in assay and related substances of the active at accelerated as well as two long term conditions. The viscosity values were not significantly altered during the stability of the product and there were no significant differences in the dissolution rates at 30 minutes time interval from initial values during the stability period under evaluation. Thus, the data indicates the quality of the product remains within the specified limits for 6 months at accelerated condition and upto 36 months at long term conditions.

The developed oral jelly of MH look as shown in figure 4

Figure 4: Image of oral jelly of MH

4.2.2 Development and evaluation of Teneligliptin Oral Jelly Containing MH Extended Release Pellets

A combination of MH in extended release form and THH in immediate release form in terms of tablets lead to large size of the tablets, as depicted in table 2 below.

Table 2: Examples of marketed tablets of MH and THH with unit weights and dimensions

Sr. No.	Product Name	Average Weight	Length	Width	Thickness
1	Tiban M 20/1000 mg	1705.0 mg	22.16 mm	11.10 mm	7.81 mm
2	Tiban M 20/500 mg	990.0 mg	19.70 mm	9.16 mm	6.15 mm
3	Zita-Met Plus 20 mg/1000 mg	1587.0 mg	20.92 mm	10.85 mm	8.02 mm
4	Ziten M 20 mg/500 mg	1115.0 mg	19.90 mm	8.42 mm	7.07 mm

From table 2 it can be seen that all tablets in stated examples are exceeding the length 17 mm in dimensions. As per guidance from USFDA we need to restrict the dimensions above 17 mm, to avoid difficulty in swallowing. Especially for chronic and geriatric patients it is very difficult to administer such large sized tablets. Hence it was decided to develop oral jelly containing these actives to provide similar release (extended release for MH and immediate release for THH) for patient compliance.

The product development involved two portions, development of THH portion and development of MH coated pellets

Development of THH portion:

Initial feasibility trials were conducted to select suitable viscosity increasing agent from carbomer, iota carrageenan and sodium carboxymethyl cellulose (SCC).

THH was found incompatible with carrageenan and carbomers resulting in precipitation and loss of jelly structure. This may be due to acidic nature of drug. However, jelly with 1% w/w concentration of SCC did not show any precipitation. Thus, SCC was selected as viscosity building agent. SCC has pH independent solubility and cold water can be used for its processing making commercially suitable.

Since the oral jelly is meant for diabetic population, an artificial sweetener sucralose was considered for product development. Sucralose is safe for use in all, including patients having diabetes (Tandel 2011)**.**

THH does not have any challenge related to obnoxious taste. However, to impart an elegant and attractive look and good taste to the formulation, peppermint flavour was added and light blue colour was added to the formulation through Brilliant blue FCF. Methyl paraben and propyl paraben were selected as preservatives.

THH was dissolved in water, sucralose was added to it and kept aside. Methyl paraben and propyl paraben were dissolved in water at about 80ºC to 90ºC and allowed to cool. Peppermint flavour was dispersed in propylene glycol. In separate quantity of water, SCC was dispersed and allowed to soak for about 1 hour. It was mixed under stirrer and it was ensured that lump free dispersion is formed. This colloidal dispersion was then followed by addition of Brilliant blue FCF to drug solution under stirring. Preservatives solution and flavour solution were added to the drug solution to form bulk, under stirring and kept aside. pH was adjusted with 0.1N HCl to about 4.5 and weight was made up with water.

Development and manufacturing process of MH pellets portion

MH is highly soluble thus release retardant to provide extended release is required in core pellets. Carbopol 974P, SCC (Cekol 100000) and other polymers were tested during feasibility trials. Methocel K200M CR was found superior to carrageenan.

In case of THH portion without any viscosity imparting agent, MH coated pellets were settled in the translucent jelly of THH, as shown in figure 5 and figure 6

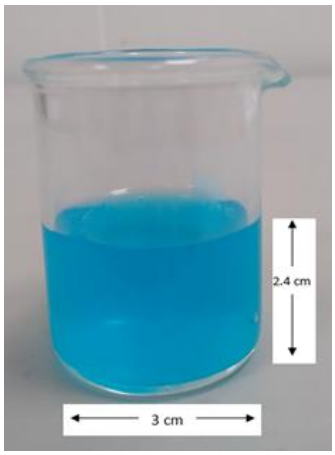


Figure 5: THH portion without MH coated pellets

Figure 6 Settled MH pellets

Therefore, in subsequent trials sodium CMC was added to the formulation to avoid settling of pellets. It was also observed that uncoated MH pellets or pellets coated with only release retardant viz. Eudragit RL 30 D welled after a few hours of immersing in THH jelly. This indicated, additional protection to the release retardant coating needed to be given to protect

the coated pellets in aqueous environment. Considering acidic nature of THH, it was thought that, an enteric coating over release retardant coating would help for aqueous stability in THH jelly. This coating provides additional benefit of exhibiting extended release.

It was decided to optimize the formula of MH pellets by conducting design of experiments using 2 level three factors viz. the quantity of matrix forming agent Methocel K200M CR (150 mg – 250 mg), percent weight gain of extended release coating (10% w/w– 30% w/w) and percent weight gain of aqueous protection coating over extended release coating (20% w/w– 30% w/w) with three centre points. Responses were measured for the experiments to get data of friability, aqueous stability, % cumulative release at 1 hour, % cumulative release at 3 hours and % cumulative release at 10 hours, The experimental design was evaluated for various parameters, to check ANOVA table, presence of any curvature and if model was significant.

The responses viz. pellets friability, aqueous stability of coated pellets, % cumulative release at 1 hour, 3 hours and 10 hours were evaluated statistically through the Design Expert software and the data were used to get optimized formulation from design space.

For manufacturing of coated pellets of MH, microcrystalline cellulose, hydroxypropyl methylcellulose (Methocel K200M CR) and povidone were blended in a rapid mixer granulator. To make a wet mass, water was added under mixing. The extrusion of wet mass was carried out using 0.8 mm screen of extruder. Spheronization was performed using 3.25 mm chequered plate at 400 to 800 rpm. The formed pellets were dried at 55ºC till loss on drying (LOD) value below 2.0% w/w. Extended release coating was performed using bottom spray technique using Eudragit RL 30 D, triethyl citrate, talc and water with about 20% w/w solid contents in the liquid dispersion, over core pellets as substrate. Aqueous protection coating was performed using bottom spray technique using Eudragit L 30 D 55, triethyl citrate, talc and water as 20% final dispersion, over ER coated pellets as substrate. Optimized pellets were dispersed in THH jelly.

The resultant optimized composition of 20/1000 mg strength and lower strength i.e. 20/500 mg were prepared by dispersing dose weight proportional quantity of MH coated pellets in THH jelly to get 15 g formulation. Thus, the target weight for both 20/1000 mg strength and 20/500 mg strength was kept as 15 g.

MH coated pellets weighing 2139.05 mg were mixed in THH jelly to give 20/1000 mg strength whereas half the amount of pellets when mixed with THH jelly gave 20/500 mg strength combination jelly in 15 g total unit weight respectively.

The optimized formulations were incubated in stability as per ICH storage conditions (40°C/75% RH as an accelerated conditions, 30°C/75% RH and 25°C/60% RH as long term conditions) in unit sachets of triple laminated aluminium foil for 20/500 mg and 20/1000 mg strengths.

Scale up of MH pellets from laboratory scale:

The pellets of MH, being of modified release nature, were scaled up from lab to a pilot scale to check the scale up impact and to evaluate robustness of the optimized pellets formulation. Scale up was carried out using a 100 L rapid mixer granulator (RMG), twin screw extruder of 80 mm diameter (dome type), 700 mm spheronizer and fluidized bed processor of 110L capacity bottom spray bowl (make: Anish Pharma Equip Pvt. Ltd., Nashik, Maharashtra, India).

Evaluation of oral jelly with pellets

Physical observation: The jelly formulations were evaluated visually for odour, clarity, texture and for presence of undesired foreign particles. By mild rubbing jelly between two fingers, grittiness and stickiness were evaluated.

Weight variation: Weight variation from ten individual sachets was determined. The jelly was squeezed out from sachets and weighed by difference for this purpose.

Viscosity measurement: For measuring the viscosity, viscometer (model: Brookfield DV3TLV) was used. Helipath mode using T bar spindle no. 96 was selected for this high viscosity jelly. Viscosity at 25°C, was checked, using 250 g jelly, in triplicate readings. Value near torque of 50 was treated as the reading.

pH measurement: For measuring pH of jelly, pH meter (make: Lab India) was used at 25°C. Duplicate readings were taken and average was treated for evaluation purpose.

To determine pH, 0.5 g of formulation was added to 50 mL purified water, mixed and then pH was measured.

Syneresis: Syneresis or de-swelling may be observed in jellies because of release of liquid, leading to shrinkage of jelly structure and reduced quality. It is reported that it may be pronounced in the formulations containing less concentration of viscosity increasing agent. The formulation trials were checked for any tendency of syneresis.

Aqueous stability of MH coated pellets: The experimental trials were visually checked for aqueous stability of the MH coated pellets and scores in the scale of 1 to 5 were assigned. Oral jelly was placed in a clear transparent glass beaker of 100 mL capacity and viewed for swelling of embedded pellets after one week, against the board having illuminated black and white background. Visual observation of all experiments was noted and scoring was given, 5 being the highest, showing no swelling.

Dissolution rate:

Extended release formulation of MH with immediate release THH combination does not appear in any pharmacopoeia. Thus, for dissolution of THH component, Indian Pharmacopoeial method for THH tablet was used. For dissolution of MH, United States Pharmacopeial method for extended release MH tablet was referred. Weighing of THH and MH jelly was done by difference. The test of dissolution rate was performed for each active, using conditions mentioned below:

For THH:

Dissolution was carried out in 900 mL purified water using paddle at 50 rpm at 37± 0.5 °C.
Marketed THH tablets (Tenelia 20) were also evaluated for the dissolution using same conditions to have a comparative set of data.

The aliquots were periodically withdrawn to estimate the quantity of active released by HPLC method (Make of instrument- Agilent Technologies Ltd, India).Chromatographic conditions for dissolution test were kept same as of the assay.

For MH:

Dissolution for MH part was carried out in 1000 mL pH 6.8 phosphate buffer using basket at 100 rpm at 37°C.

The aliquots were periodically withdrawn at 1 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr and 12 hr and quantity of active released evaluated by UV method at λmax 232 nm (Make of instrument- Agilent Technologies Ltd, India). The similarity factor was found out by comparing dissolution profiles with marketed formulations (Glucophage XR) to check if the prepared formulations were comparable in vitro.

Similarly dissolution was also carried out with marketed bilayered Tiban M tablets in both dissolution media and compared with developed formulation for both strengths.

Assay:

For THH from oral jelly:

Assay of THH was performed using an HPLC method. The sample was collected from 5 sachets and equivalent to about 20 mg THH was diluted with water to get 20 ppm concentration. The measurement was performed using HPLC with UV detector (Agilent 1260 Infinity) using Zorbax SB C8 (150 X 4.6 mm, 5µm) at flow rate of 1 ml/min at 246 nm, comparing against the same concentration of standard solution. Column temperature was kept 40°C ± 2°C and injection volume was 20 µL.

For MH from oral jelly:

For measurement of assay, sample equivalent to about 100 mg MH, collected from 5 sachets was weighed and diluted using water to get 10 ppm concentration. Standard solution of same concentration was prepared. The absorbance of standard and sample preparation was measured at 232 nm in 1 cm cell against water as blank using a UV spectrophotometer.

Table 3 mentions the main effects observed, either alone or as combination of 3 factors studied, for respective responses for composition of MH pellets.

Related substances:

Related substances method of MH extended release tablets was referred from USP monograph and was used for evaluation of related substances for MH with minor

modifications. An in house method was developed for evaluation of related substances for THH from the oral jelly formulations.

Table 3: Different responses and main effects

Sr. No.	Responses	Main Effects
1	Friability (%)	B, A, C
2	Aqueous stability (score)	C, B
3	% Cumulative release at 1 hour (%)	C
4	% Cumulative release at 3 hours (%)	B, A
5	% Cumulative release at 10 hours (%)	BC

Note: A= Methocel K200M CR, B: ER coating, C= Aqueous protection coating, AB, AC and BC being the interaction terms between the main factors

The observed 3 D graphs using the software for all the responses are depicted in figure 7.

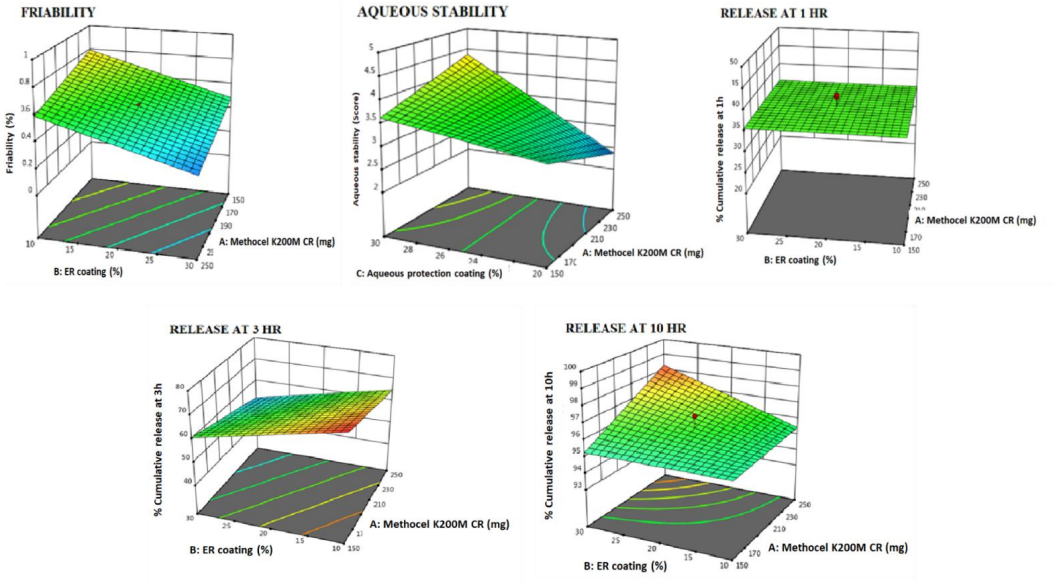

FRIABILITY
Friability (%)
A: Methocel K200M CR (mg)
B: ER coating (%)
AQUEOUS STABILITY
Aqueous stability (score)
A: Methocel K200M CR (mg)
C: Aqueous protection coating (%)
RELEASE AT 1 HR
% Cumulative release at 1h
A: Methocel K200M CR (mg)
B: ER coating (%)
RELEASE AT 3 HR
% Cumulative release at 3h
A: Methocel K200M CR (mg)
B: ER coating (%)
RELEASE AT 10 HR
% Cumulative release at 10h
A: Methocel K200M CR (mg)
B: ER coating (%)

Figure 7: 3 D surface graphs of all responses

As indicated in the 3D graphs, as % ER coating increases, the friability decreases. This may be due to the hard nature of coating protecting the inner cores. On the other hand, as

concentration of Methocel K200M CR increases, the % friability decreases. Aqueous stability increases as % of aqueous protection coating increases. It is also observed that at lower % of aqueous protection coating, as concentration of Methocel K200M CR increases, the aqueous stability decreases, however, gradually increasing aqueous protection coating along with increased concentration of Methocel K200M CR gives increased aqueous stability. Hence we observe a twisted 3D graph. Regarding release at 10 hour, as % ER coating increases, the release is unaffected, however, when both % ER coating and concentration of Methocel K200M CR increase together, the release at 10 hour increases. Therefore we observe a twisted 3D surface graph. For the remaining 3 D graphs we observe linear relationships, at specific slope.

After the thresholds were assigned to get desired parameters, the data were fed in the DOE software to get design space, as shown in figure 8.

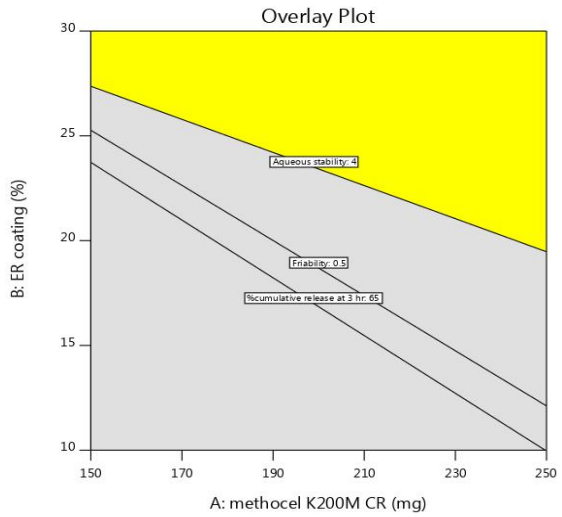
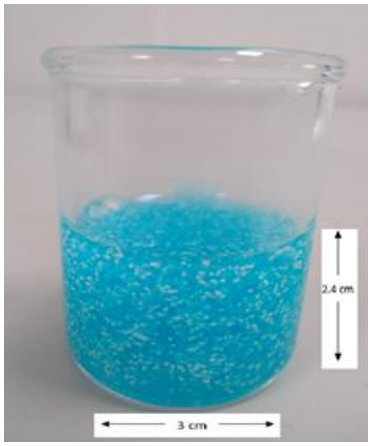


Figure 8: Design space for arriving at optimized formulation of extended release pellets of MH for oral jelly containing THH in dissolved form

Derived through the design space observed to follow predicted responses as per the design space.

The optimized formulations images are as shown in figure 9 and figure 10 for 20/500 mg strength and 20/1000 mg strength respectively.



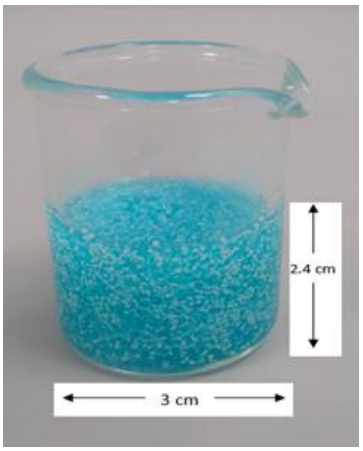


Figure 9: Image of 20/500 mg strength **Figure 10: Image of 20/1000 mg strength**

In-vitro release profiles:

In vitro release profiles of two actives in the optimized formulation were compared against respective individual reference tablets product from the market. The comparative in vitro release profiles for THH are as shown in figure 11-I and figure 11-II, for 20/1000 mg strength and 20/500 mg strength respectively. Similarly, the comparative in vitro release profiles for MH are as shown in figure 11-III and figure 11-IV, for 20/1000 mg strength and 20/500 mg strength respectively. A slightly higher drug release was observed initially, i.e. at 5 min. and 10 min from jelly formulation when compared with reference tablets (Tenelia 20) and Tiban M tablets. This could be because the active is in dissolved form in case of jelly formulation, while the tablets need to disintegrate first in order to release the active. When extended release profiles of MH were compared, the release from pellets suspended in jelly were slightly faster than reference tablets (Glucophage XR) whereas similar to that of from bilayered tablet. However, the release profile was well within the limits specified in USP monograph for MH extended release tablets. During stability, both 20/1000 mg and 20/500 mg strengths were found to be stable upto six months at accelerated and eighteen months at long term stability conditions as per ICH conditions. No significant change in description, assay, related substances and dissolution were found.

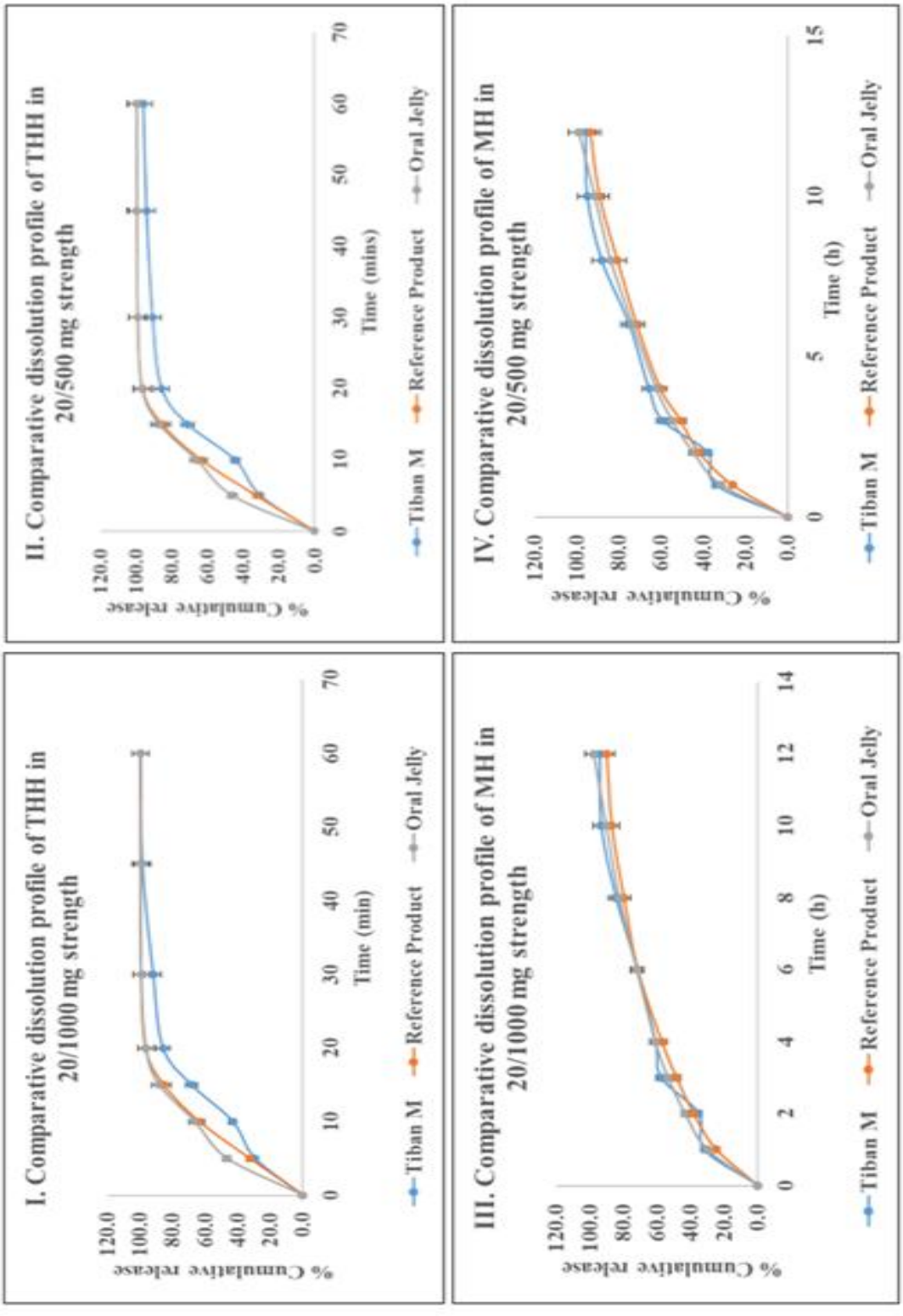


Figure 11: Comparative dissolution profiles of THH and MH in 20/1000 mg and 20/500 mg strength (n=6)

4.2.3 Development and evaluation of MH Immediate Release Pellets

Current study involves development of alternate dosage form of MH in pellets form for sprinkle application to improve patient compliance in patients suffering from dysphagia.

MH has inherent bitter taste, therefore, taste masking would be the primary challenge for the pellets dosage form. To make it more palatable, addition of flvaour and artificial sweetener may be required. Sucralose as a non caloric artificial sweetener was used. Capsaroma Flavour Peppermint DC 117 was selected to enhance the palatability of the pellets formulation. As a primary pack, triple laminated sachet was thought to be a good choice. The users can carry these unit dose sachets in their pockets or purses.

MH in immediate release pellets as an alternate dosage form in place of large size tablets was targeted to be developed. The pellets would be sprinkled over soft food for ease of administration at user's end. Use of extrusion spheronization to form pellets is one of the known method which is preferred in case of high drug content rather than drug loading over inert substrate. However, a few challenges were identified during development of the product. The first challenge was related to bitter nature of MH. The second challenge was to give spherical shape to the pellets, yet to limit the size of the pellets to comply with the guidance laid down by USFDA about, size of beads for sprinkle application.

Initial trials were conducted using different binders, to check if the shape of the pellets can be achieved towards spherical shape, by altering various process parameters such as spheronization speed and time.

For coating of the rod shaped pellets of MH, sucralose was dissolved in water under stirring using over head stirrer. Then Opadry AMB II 88A180040 White was added in vortex, allowed to mix for about 40 minutes. It was filtered through ASTM #100 sieve.

Bottom spray coating was performed using GPCG 1.1 (Make: ACG-Pam Glatt) using plate B of bottom plate, 1.0 mm nozzle and PC satin retention bag. Product temperature was set at about 45ºC.

To arrive at the best possible composition, a statistical way in the form of design of experiments (DOE) was adapted. For optimization of the formulation, quantity of povidone (30 mg to 90 mg), quantity of sucralose in coating (12 mg to 24 mg) and amount of coating over core pellets (120 mg to 240 mg) were treated in Design Expert software, as three factors.

Experiments were planned using a two level, three factorial design using three centre points. Total 11 experiments were planned. Four responses viz. bulk density, sweetness, bitter taste masking and description were evaluated and fed the data in the software to arrive at design space. The optimized composition was selected from the obtained design space.

Preparation of core pellets:

Extrusion spheronization process involved granulation, extrusion, spheronization, drying, sizing as unit processes. MH, microcrystalline cellulose and povidone were sifted through #40 ASTM mesh and transferred to rapid mixer granulator. Mixing of this portion was done at 50 rpm of mixer for 10 minutes. Granulation was done using addition of purified water. Water uptake of about 11.6% w/w of the dry mix was required to achieve the desired end point for appropriate extrusion through the extruder. The wet mass achieved through the granulation process was fed to the single screw, cone type extruder fitted with 0.6 mm screen. The extrudes were observed to be of about 10 mm to 12 mm in length. They were fed to spheronizer of 250 mm diameter. Spheronizer speed of about 800 rpm was used and spheronizer time about 4 minutes was kept for experimental trials. Drying of the pellets was done at 50º C for about 20 minutes to keep loss on drying less than 2.0% w/w. Drying was done in fluidized bed dryer (make: Retsch TG200).

Coating of core pellets in fluid bed processor:

The dried pellets were sized to get substrate (passed through #25 ASTM mesh, retained on #40 ASTM mesh), over which the coating of aqueous moisture barrier (AMB) coating with sucralose would be applied. 'B' distribution plate of bottom spray assembly of fluid bed processor (make: GPCG 1.1 by ACG) was selected. PC satin bag was used as retention bag in the chamber of the equipment. The substrate was coated with the coating at product temperature between 45º C to 50º C.

For easy flow through the sachets, blending of pellets with sifted (through #40 ASTM mesh) colloidal silicon dioxide, talc, Capsaroma Flavour Peppermint DC 117 and sucralose was done in a blender and filled as per unit weight in triple laminated sachets (12 Micron polyester/9 Micron aluminium/63 Micron polyethylene). The experimental trials were planned using Design of Experiments statistical software.

The average weight for 1000 mg strength was kept as 1390 mg. Likewise, average weight for 500 mg was half the weight of 1000 mg, that is 695 mg. The optimized formulation arrived after running the data through DOE software was incubated for stability according to ICH

conditions (accelerated conditions as 40℃/75% RH and long term conditions as 30 ℃/75% RH and 25 ℃/60% RH) in primary pack in terms of triple laminated sachets for both strengths 500 mg as well as 1000 mg.

Evaluation of MH pellets

Description: It was observed during initial experimental trials that we can not get spherical shaped pellets for MH, the nature of pellets in terms of its surface texture and overall appearance was evaluated visually and scored between scale of 1 to 5. 5 was considered as the highest score assuming the most desired shape of the pellets with good surface texture.

Bulk density: Bulk density was considered an important factor for controlling volumetric fill volume in the sachets. Higher the density, better the coating efficiency and subsequently smaller fill volume for the unit dose. Bulk density was measured as per the general chapter of USP.

Sweetness: Quantity of sucralose was considered as one of the factor in DOE experimental trials. The sweetness was perceived by team of volunteers. The scoring was given in the range of 1 to 5. Highest score was assigned to most desired sweetness level.

Bitter taste masking: Since MH has inherent bitter taste, this was considered as one of the responses in DOE study. Bitter taste masking was perceived by the same team of volunteers at the time of measurement of sweetness and scoring was given in the range of 1 to 5. Highest score was assigned to most desired masked level of bitter taste.

Assay: For measurement of assay, sample equivalent to about 100 mg MH, collected from 5 sachets was weighed and diluted using water to get 10 ppm concentration. Standard solution of same concentration was prepared. The absorbance of standard and sample preparation was measured at 232 nm in 1 cm cell against water as blank using a UV spectrophotometer.

Related substances: Related substances method of MH extended release tablets was referred from USP monograph and was used for evaluation of related substances for MH with minor modifications.

In-vitro dissolution: MH pellets are not a part of any pharmacopoeia. Dissolution conditions of MH tablets of United States Pharmacopeia were partly referred. Individual sachet was weighed and dissolution rate test was carried out using USP type I (basket) apparatus, using pH 6.8 ± 0.05 phosphate buffer, 1000 mL, 100 rpm, at 37 ± 0.5 °C. The analyte was measured using UV spectrophotometry (λmax of 232 nm); (Spectrophotometer make- Agilent

Technologies Ltd, India). To get comparative in vitro dissolution data, commercialized tablets were evaluated by using same method. Periodically samples were collected and drug release was estimated by using UV spectrophotometry (at λmax of 232 nm); (Spectrophotometer make- Agilent Technologies Ltd, India).

Table 4 mentions the important significant effects observed, either individual or in combination of the three factors for the respective responses.

Table 4: Main effects for different responses

Sr. No.	Responses	Main Effects
1	Description	A, B, AB
2	Bulk density	A
3	Sweetness	B
4	Bitter taste masking	C

Note: A= povidone, B: sucralose, C= coating over pellets, AB being the interaction term between A and B

The 3 D graphs observed for all responses are shown in figure 12.

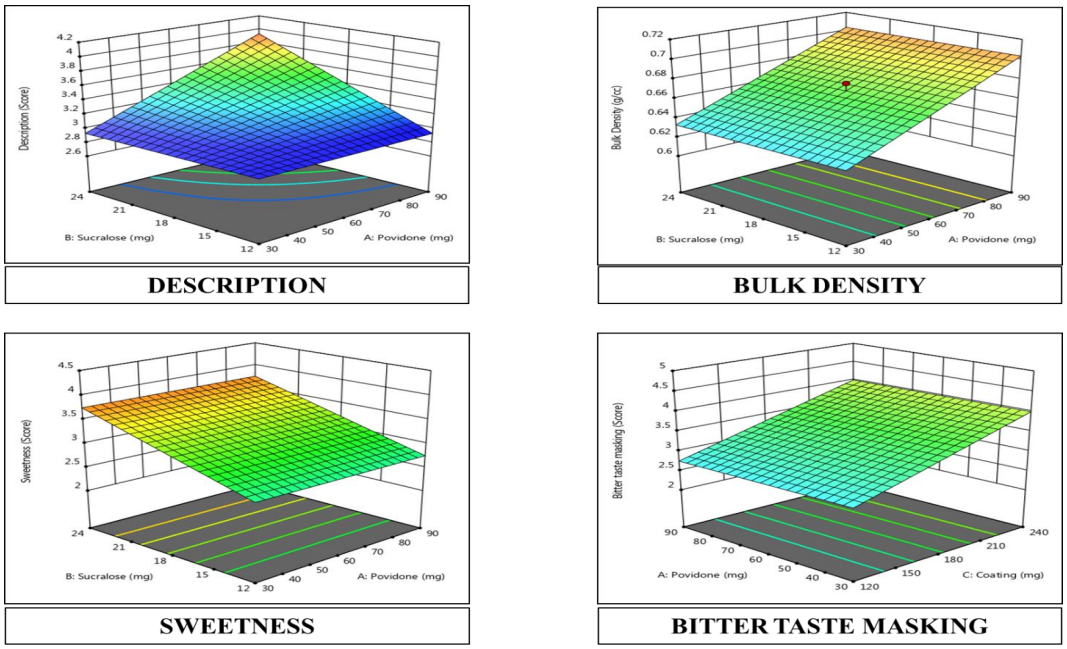


Figure 12: 3 D surface graphs of all responses

After the data were put in DOE software, and the thresholds were applied to get most desired parameters, design space was obtained as shown in figure 13. Optimized composition was selected from the design space.

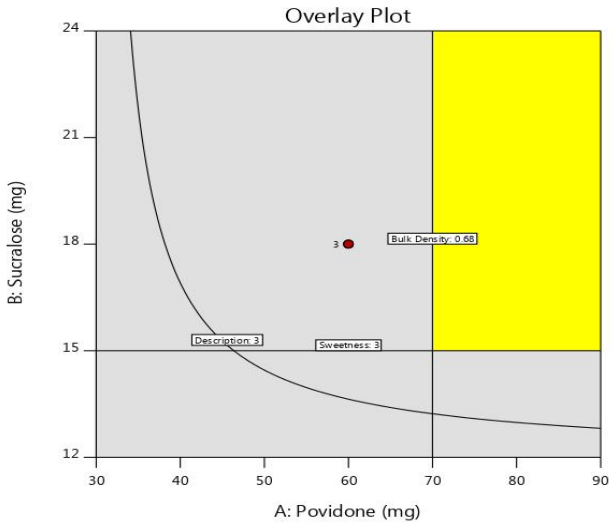


Figure 13: Design space for obtaining optimized formulation of immediate release pellets of MH

The concentrations of povidone, sucralose and the coating weight gain were chosen from the design space and this optimized formulation was incubated for stability.

The dissolution profile of the optimized composition was compared with the reference product (tablets) available in the market. In vitro release profiles for MH for both test and reference products are as shown in figure 14 and figure 15, for 1000 mg strength and 500 mg strength respectively.

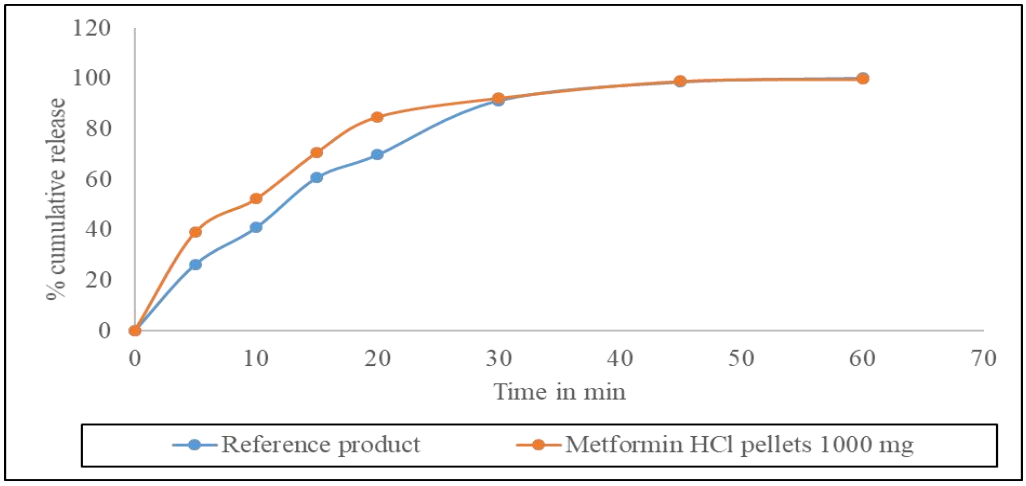


Figure 14: In vitro dissolution profile of MH pellets Vs. reference tablets for 1000 mg strength

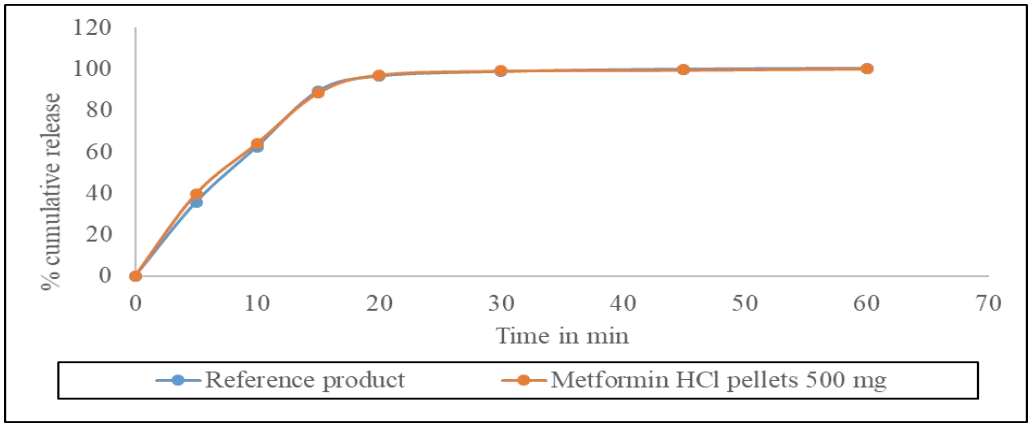


Figure 15: In vitro dissolution profile of MH pellets Vs. reference tablets for 500 mg strength

Figure 14 and figure 15 denote the comparative dissolution profile of MH pellets against marketed reference product as tablets. For 1000 mg the dissolution profile from pellets was found to be slightly faster at initial time points of 5, 10, 15 and 20 min. and there was no significant difference observed, compared with the tablets formulation and this may be due to large surface area of pellets against the tablets. For 500 mg strength the dissolution profile of MH pellets was similar to reference tablets. This may be due to better sink condition of lower strength in the dissolution medium for reference tablets. All these dissolution profiles were within limits mentioned in MH tablets monograph in USP. When the optimized formulation was scaled up, a slightly different parameters needed to be followed as per the equipment capacities, for example, rpm and time of spheronizer at scale up level needed to be kept at lower values to achieve desire physical appearance of the pellets. At higher values of rpm and time it was observed that a lot of fines were getting generated leading to loss of yield, and the nature of the pellets did not change from slightly cylindrical shape. There was no significant difference between lab scale batch and scaled up batch with respect to granulation point, water uptake during granulation, nature of extrudes and spheronized pellets, loss on drying value after drying the pellets, particle size distribution and bulk and tapped density of the pellets. There was no significant difference noticed in coating process parameters of product bed temperature and nature of pellets for aqueous moisture barrier coating using bottom spray technique. Necessary column height, inlet temperature, atomization air, bottom distribution plate combination, velocity of the air, spray rate needed to be set on the scale up equipment to

achieve desired coating process. The physico chemical parameters for scale up batch was found to be similar to trial batch. The developed immediate release pellets of MH look as shown in figure 16.

During stability testing, both 1000 mg and 500 mg strengths were found to be stable upto six months at accelerated and eighteen months at long term stability conditions as per ICH conditions. No significant change in description, assay, related substances and dissolution were found.

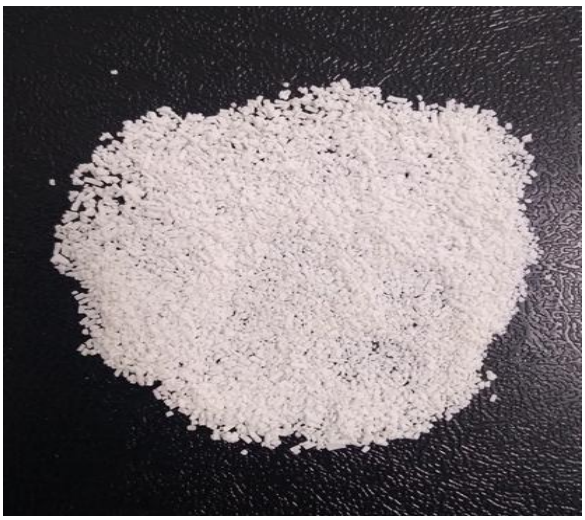


Figure 16: Image of immediate release pellets of MH

4.2.4 Development and evaluation of MH Extended Release Pellets

MH pellets having extended release profile for sprinkle application was thought to be an important dosage form for use in dysphagic diabetic patients. It is obvious that, when high strength such as 1000 mg per unit of this active and excipients including release retardants (to release the active over extended period of time), would make the dosage form bulky in size. Such compressed tablets would definitely face problem for swallowing for chronic patients, especially to geriatrics. Following examples of a few marketed formulations of MH Extended Release Tablets make it realize that patients may need a better option to overcome difficulty in swallowing.

Table 5: A few examples of MH extended release tablets in Indian market

Sr. No.	Product Name	Average Weight	Length	Width	Thickness
1	Glycomet – 1 GM	1351.0 mg	20.41 mm	9.73 mm	7.82 mm
2	Glycomet – 500 SR	716.0 mg	15.09 mm	8.63 mm	6.81 mm

3	Metsmall 1000	1326.0 mg	19.90 mm	8.42 mm	7.07 mm

Current study involves development of extended release MH in pellets form for sprinkle application to improve patient compliance in patients suffering from dysphagia. This was targeted to comply to the USFDA guidance related to size of the beads labelled for sprinkle application. It was also developed to enable users to carry the sachets in their pockets or purses for convenience.

Formulation development approach:

As per the prior art and experience on high strength pellets process, the suitable process of manufacturing to follow was by extrusion and spheronization technique and provide extended release coating to retard the release of MH. Due to this coating the bitter taste of the core containing MH would be masked. To make it more palatable, addition of flvaour and artificial sweetener may be required. Use of sucralose as a non caloric artificial sweetener was preferred. Orange Flavour 844763 (Tang orange flavour) was selected to enhance the palatability of the pellets formulation. As a primary pack, triple laminated sachet was thought to be a good choice. The users can carry these unit dose sachets in their pockets or purses.

It is expected that the pellets after extrusion and spheronization process of the wet mass be of round shape, so that the coating if any to be applied over core pellets would be uniform. Therefore, feasibility trials were taken to achieve desired dissolution profile with near to rounded pellets, using different release retardants such as Hydroxypropyl Methylcellulose IP (Methocel K200M CR), Ammonio Methacrylate Copolymer, Type A (Eudragit RL 30 D), Ammonio Methacrylate Copolymer, Type B USPNF (Eudragit RS 30 D), Ethyl acrylate and methyl methacrylate copolymer dispersion USPNF (Eudragit NE 30 D), Sodium carboxymethyl cellulose (KDA8M20), Sodium carboxymethyl cellulose (Cekol 100000), Kappa Carrageenan, Carbomers (Carbopol 971P and Carbopol 974P) ethyl cellulose. After having desired shape of the pellets, they would be targeted to release MH as per limits mentioned in USP monograph of MH extended release tablets. The dissolution rate limits are as mentioned in table 6.

Table 6: Dissolution profile limits for MH extended release tablets

Time in hours	% cumulative release (for 500 mg)	% cumulative release (for more than 500 mg)
1	20 – 40	22 – 42
3	45 – 65	49 – 69

10	NLT 85	NLT 85

Table 7: Dissolution profile of coated MH extended release pellets compared with cores

Time in hrs (limits)	SK2020007 (core)	SK2020007A (5% w/w)	SK2020007B (15% w/w)	SK2020007C (25% w/w)
1 (25-40)	42.2	39.8	34.6	31.2
3 (50-65)	72.7	66.8	58.5	54.9
10 (NLT 85)	97.7	96.9	97.0	96.8

B. No. SK2020007C was reproduced again as B. No. SK2020009, blended with extragranular ingredients such as colloidal silicon dioxide, talc, Orange Flavour 844763 (Tang Orange Flavour), sucralose and incubated for stability. Coated pellets of MH were prepared as dose weight proportional formulae hence both 1000 mg and 500 mg strengths have divisible compositions with average unit weights of 1811 mg and 905.5 mg respectively.

Description: Since it was observed during initial experimental trials that we can not get spherical shaped pellets for MH, the nature of pellets in terms of its surface texture and overall appearance was evaluated visually. The taste of the pellets was completely masked due to coating, however, for palatability the added ingredients such as sucralose imparted sweet taste and tangy orange perception due to flavour.

Bulk density: Bulk density was considered an important factor for controlling volumetric fill volume in the sachets. Higher the density, better the coating efficiency and subsequently smaller fill volume for the unit dose. Bulk density was measured as per the general chapter of USP.

Assay: Assay of MH extended release pellets was performed as mentioned for MH immediate release pellets, by UV spectroscopy.

Related substances: Related substances method of MH extended release tablets was referred from USP monograph and was used for evaluation of related substances for MH with minor modifications

In-vitro dissolution: MH pellets are not a part of any pharmacopoeia. Dissolution conditions of MH tablets of United States Pharmacopeia were partly referred. Individual sachet was weighed and dissolution rate test was carried out using USP type I (basket) apparatus, using

pH 6.8 ± 0.05 phosphate buffer, 1000 mL, 100 rpm, at 37 ± 0.5 °C. The analyte was measured using UV spectrophotometry (λmax of 232 nm); (Spectrophotometer make- Agilent Technologies Ltd, India). To get comparative in vitro dissolution data, commercialized tablets were evaluated by using same method. Periodically samples were collected and drug release was estimated by using UV spectrophotometry (at λmax of 232 nm); (Spectrophotometer make- Agilent Technologies Ltd, India). The samples were withdrawn at periodic intervals for in vitro evaluation of the pellets.

In vitro release profiles for MH for both test and reference products are as shown in figure 17 and figure 18, for 1000 mg strength and 500 mg strength respectively.

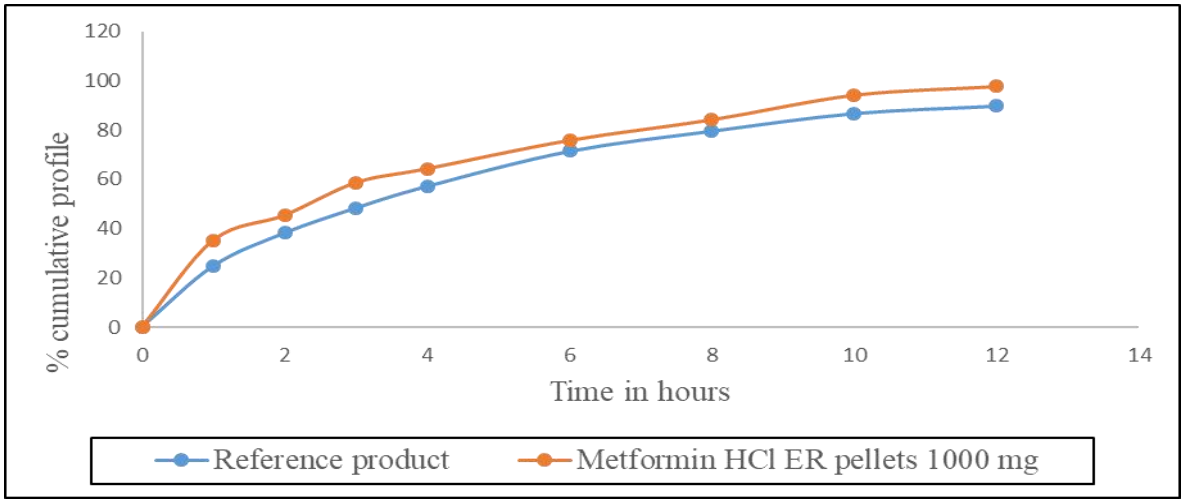


Figure 17: In vitro dissolution profile of MH ER pellets Vs. reference tablets for 1000 mg strength

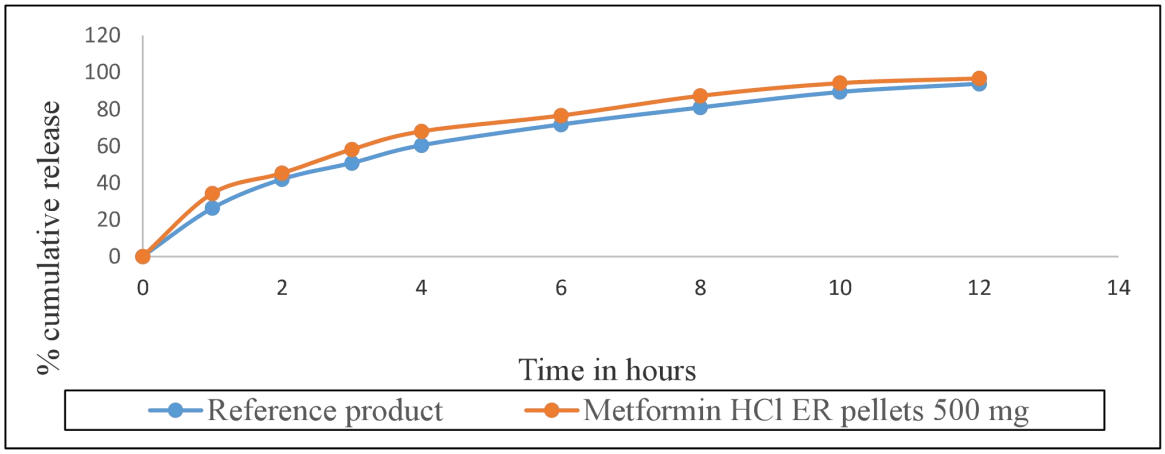


Figure 18: In vitro dissolution profile of MH ER pellets Vs. reference tablets for 500 mg strength

Stability of the product:

Both 1000 mg and 500 mg strengths were found to be stable upto six months at accelerated and eighteen months at long term stability conditions as per ICH conditions. No significant change in description, assay, related substances and dissolution were found.

During development of MH extended release pellets, initial trials were focused on the rounding of the pellets. Three different types of Eudragit dispersions viz. Eudragit RL 30 D, Eudragit RS 30 D and Eudragit NE 30 D were tried as granulating fluid as well as release retardants in the composition. Sodium carboxymethylcellulose, of two grades viz. KDA8M20 and Cekol 100000 were used in subsequent feasibility trials, as release retardants. Kappa carrageenan and Methocel K200M CR were also tried as release retardant and to check their capability to give spherical shape in spheronizer. Out of the experiments taken, trials with kappa carrageenan and Methocel K200M CR gave pellets with rounded edges. Core as well as coated pellets using Kappa carrageenan however, could not achieve the desired release profile. Coated pellets containing methocel K200M CR at different coating weight gain were checked for release profile and the composition with 25% w/w was decided to be the optimized formula to charge on stability for evaluation. As observed in figure 16 and figure 17, both 1000 mg and 500 mg strength showed similar dissolution profile of MH pellets compared with that of reference tablets. All these dissolution profiles were within limits mentioned in MH tablets monograph in USP. The developed extended release pellets of MH look as shown in figure 19.

Figure 19: Image of extended release pellets of MH

4.2.5 Development and evaluation of blend containing Granules of THH in Immediate Release Form and MH Pellets in Extended Release Form

The combination of antidiabetic drugs where MH is in extended release form, makes the dosage form bulky and large in size as mentioned in earlier section.
In current study, the combination of THH and MH for sprinkle application was thought to be useful from patient compliance point of view.
Since THH needs to be released in immediate release form and MH in extended release form, these two parts were developed separately and mixed together to have one single blend. MH portion was used with the same composition as described in Section 4.4. THH does not have any bitter or obnoxious taste and hence taste masking strategy was not required. However, to make the entire blend palatable, artificial sweetener and flavouring agent were added. As a primary pack, triple laminated sachet was thought to be a good choice. The users can carry these unit dose sachets in their pockets or purses.

Development of THH part:

THH portion was decided to be prepared by simple aqueous wet granulation process using hydroxypropyl cellulose (HPC SSL). When evaluated for in vitro dissolution of these granules the release of active was not observed. Hence alternate process of slugging deslugging, which did not involve any aqueous exposure to the THH was evaluated. This dry granulation method yielded satisfactory in vitro dissolution profile showing immediate release characteristics.
Further it was investigated using X-ray diffraction and DSC studies that, during aqueous granulation and subsequent drying treatment of THH granules the form of active changes which might have led to lower dissolution results. Thus slugging-deslugging process was finalized for THH granules.
Average unit weight for optimized composition of blend containing Granules of THH in Immediate Release Form and MH Pellets in Extended Release Form for 1000 mg and 500 mg, were kept as 1911 mg and 1005.5 mg respectively.

Evaluation of Blend containing Granules of THH in Immediate Release Form and MH Pellets in Extended Release Form

Description: Blend of THH in immediate release form and MH coated extended release granules appeared as free flowing blend of granular ingredients with sweet taste and with

characteristic orange flavour. There was no bitter taste to the blend since the bitter active MH was completely coated and THH does not have any bitter taste.

Bulk density: Bulk density was considered an important factor for controlling volumetric fill volume in the sachets. Higher the density, better the coating efficiency and subsequently smaller fill volume for the unit dose. Bulk density was measured as per the general chapter of USP.

Assay of MH:

Contents of 5 sachets were collected and quantity equivalent to about 100 mg MH was diluted with water to get 10 ppm concentration.to estimate active content at λmax of 232 nm by UV spectrophotometry.

Assay of THH:

Assay of THH was performed using an HPLC method. The sample was collected from 5 sachets and equivalent to about 20 mg THH was diluted with water to get 20 ppm concentration. The measurement was performed using HPLC with UV detector (Agilent 1260 Infinity) using Zorbax SB C8 (150 X 4.6 mm, 5µm) at flow rate of 1 ml/min at 246 nm, comparing against the same concentration standard solution. Column temperature was kept 40°C $\pm$ 2°C and injection volume was kept 20 µL.

Related substances:

Related substances method of MH extended release tablets was referred from USP monograph and was used for evaluation of related substances for MH with minor modifications. An in house method was developed for evaluation of related substances for THH from the blend.

In-vitro dissolution of THH:

Dissolution was carried out in 900 mL purified water using basket at 100 rpm at 37± 0.5 °C.

Marketed THH tablets (Tenelia 20) were also evaluated for the dissolution using same conditions to have a comparative set of data.

The aliquots were periodically withdrawn to estimate the quantity of active released by HPLC method (Make of instrument- Agilent Technologies Ltd, India).Chromatographic conditions for dissolution test were kept same as of the assay.

In vitro release profiles for THH for both test and reference products are as shown in figure 20.

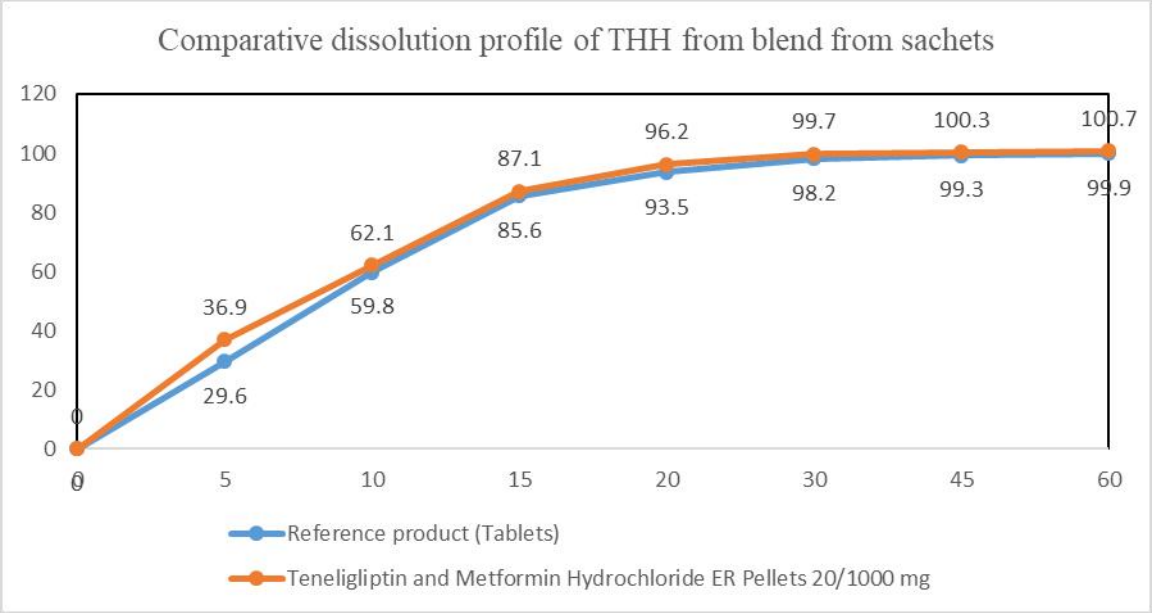


Figure 20: in vitro dissolution profile of THH from sachets and reference tablets

Stability of the product:

The stability study was conducted on optimized formulation packed in 3 ply sachets as per ICH guidelines for accelerated conditions of 40ºC/75% RH and at long term conditions of 30ºC/75% RH and 25ºC/60% RH.

Both 20/1000 mg and 20/500 mg strengths were found to be stable upto six months at accelerated and eighteen months at long term stability conditions as per ICH conditions. No significant change in description, assay, related substances and dissolution were found.

The developed blend of granules of THH in immediate release form and MH pellets in extended release form look like as shown in figure 21.

Figure 21: Image of blend of granules of THH in immediate release form and MH pellets in extended release form

4.3 In silico evaluation of actives from the dosage forms by compartmental modelling

Evaluation version of GastroPlus was used for treating in vitro data of all developed formulations.

As per GastroPlus software the compartmental distribution of actives from different dosage forms in various organs was predicted.

5 SUMMARY

- Inspiration of topic was taken from USFDA's guidance on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules. Active with large dose requirement (MH) alone and with its combination with THH was selected for development.
- Oral jelly and pellets in sachets were selected as alternative dosage forms of MH and THH
- Total five products were developed and two approaches were discontinued during study duration.
- Analytical method development and validation was carried out considering the all the dosage forms developed. These methods were used for preformulation as well as stability testing of the dosage forms.
- Design of experiments approach was used for majority of product development approaches.
- In Silico evaluation of dosage forms was carried out using GastroPlus software.
- Scale up at 50X level was carried out for pellets coating process using bottom spray technique. Thus the scalability of the developed products at commercial level is assured.
- The products were evaluated for costing to check economical feasibility.
- Three patent applications were filed and published and one patent from these, is granted.

6. PUBLICATIONS, PRESENTATION AND PATENT APPLICATIONS

Please find below the details of the outcomes from Ph. D. programme.

Publications

Sr. No.	Type of publication	Name of Journal	Impact factor	Title of publication	Status
1	Review article	Journal of Drug Delivery Science and Technology	3.981	Review on: Alternatives to large dosage forms for ease of swallowing	Published (April 2020)
2	Research article	Journal of Drug Delivery Science and Technology	3.981	Oral jelly of metformin hydrochloride – Formulation development using Design of Experiments and characterization	Published (April 2021)
3	Research article	Journal of Drug Delivery Science and Technology	3.981	Development and evaluation of extended release metformin pellets suspended in teneligliptin jelly for the treatment of diabetes mellitus	Published (February 2022)
4	Research article	AAPS PharmSciTech	4.026	Design, development and scale up studies of Metformin hydrochloride multiparticulate system : A promising alternative to large size tablet	Under review at journal

Presentation

Sr. No.	Type	Name of Conference/Symposium	Title of the presentation	Presented on
1	Poster	17th international Symposium on Advances in Technology and Business Potential of New Drug Delivery System by CRS	Oral Jelly as Novel Delivery System for Metformin hydrochloride – A Practical Alternative For Difficulty in Swallowing in Diabetics	February 2019

Patent applications

Sr. No.	Patent type	Application No.	Title of the patent	Status
1	Indian patent application	378867	Oral semisolid formulations of metformin in extended release form	Granted.
2	Indian patent application	IN202021001099	Extended Release Pellets of Metformin HCl using Carrageenan for Sprinkle Application	Application is published.
3	Indian patent application	IN201921003837	Oral jelly formulations of Metformin	Application is published.

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